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10/613,990	07/08/2003	Yukiko Ishikawa	US-152O	5154

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EXAMINER	
VOGEL, NANCY S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,990	ISHIKAWA ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2005 and 10 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5-10 are pending in the case.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection that were not necessitated by applicants' amendment and therefore, this action is final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 5-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and by dependence claims 2, 3, and 5-10 are vague and indefinite in the recitation of "wherein said γ-proteobacterium has an improved ability to produce a target substance synthesized via the tricarboxylic acid cycle as compared to a wild-type γ-proteobacterium". It is not clear from the claim language whether it is intended that (1) the strain had this improved ability to produce the target substance before it was modified so that the production of ArcA protein was reduced or eliminated, or (2) the strain had this improved ability as a result of the modification affecting the production of ArcA protein. Therefore, the intended metes and bounds of the claimed subject matter

cannot be determined. The claims have been examined as if the claims clearly stated the second interpretation above.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3 and 5-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Cotter et al. (FEMS Microbiology Letters, Vol. 91, NO. 1, pp. 31-36, 1992) (previously cited).

This rejection is maintained essentially for the reasons made of record in the previous Office actions, mailed 2/10/05, slightly modified to take into consideration applicant's amendments to the claims filed 9/12/05.

Cotter et al. disclose E. coli comprising a deletion of the arcA gene, which encodes a protein ArcA, and therefore the protein does not normally function (see page 32, paragraph 1, right column, and Table 1). Since it is known that γ-proteobacterium such as E. coli possess the tricarboxylic acid cycle, and further, that the deletion of the arcA gene causes the derepression of the enzymes of said tricarboxylic acid cycle and the increase in production of products of the tricarboxylic acid cycle (see specification pages 2, lines 11-16; page 3 lines 10-25, and page 8), there is evidence that the strain disclosed by Cotter et al. which has a deletion of the arcA gene would inherently have improved production of a target substance synthesized via the tricarboxylic acid cycle as compared to a wild type γ-proteobacterium.

Applicant's arguments filed 9/12/05 and 6/10/05 have been considered, but have not been found convincing.

Applicant has argued that although Cotter discloses arcA gene disrupted strains, these strains "do not have an ability to produce a target substance synthesized via the tricarboxylic acid cycle in an amount more than an amount of the substance produced by a wild-type bacterium. In contrast, the strains used in the Examples of the present specification are modified to have an ability to produce a target substance synthesized via the tricarboxylic acid cycle. That is the WC196 strain disclosed in Example 2 is an L-lysine-producing mutant strain as described In page 9, lines 23-24 of the specification, and the MG1655ΔsucA strain in which sucA gene is disrupted is an L-glutamic acid-producing strain" (page 7 of the arguments). However, contrary to applicants arguments, it is maintained that the strain disclosed by Cotter et al. does have the ability to produce target substances, including amino acids, via the tricarboxylic acid cycle. It is clear that bacteria such as E. coli possess the enzymes of the tricarboxylic acid cycle, and produce target substances such as amino acids via this cycle, as taught in the instant application. There is evidence that the improved ability to produce such target substances would inherently result from the mutation or deletion of the arcA gene, since the instant application teaches that the ArcA protein represses synthesis of said TCA cycle enzymes, and further teaches that deletion of said gene results in increased levels of these enzymes. Increased levels of these biosynthetic enzymes would result in increased levels of "target substances" produced by these enzymes. Therefore, there is reason to believe that the mutant arcA strain disclosed by Cotter et al. would inherently

possess the property recited in the claim of improved levels of target substances when compared to the wild-type (unmodified) strain. Furthermore, the instant specification itself teaches that mutation or deletion of the arcA gene results in increased levels of production of the "targeted substances" (page 3, lines 16-26), and therefore, the strain disclosed by Cotter et al. which is arcA$^-$ would inherently produce higher levels of such targeted substances when compared to the wild type strain. There is no disclosure in the instant specification teaching that this property is limited to the WC196 or the MG1655ΔsucA strains, or similar strains (see page 6 of the specification). For these reasons, the rejection is maintained.

Claims 1-3 and 5-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Iuchi et al. (Proc. Natl. Acad. Sci. USA, Vol 85, NO. 6, pp 1888-1892, 1988) (previously cited).

This rejection is maintained essentially for the reasons made of record in the previous Office actions, mailed 2/10/05, slightly modified to take into consideration applicant's amendments to the claims filed 9/12/05.

Iuchi et al. disclose E. coli comprising a deletion of the arcA gene, which encodes a protein ArcA, and therefore the protein does not normally function (see page 1891, left column, last paragraph – right column, second paragraph, and Tables 1 and 2). Since it is known that γ-proteobacterium such as E. coli possess the tricarboxylic acid cycle, and further, that the deletion of the arcA gene causes the derepression of the enzymes of said tricarboxylic acid cycle and the increase in production of products of

the tricarboxylic acid cycle (see specification pages 2, lines 11-16; page 3 lines 10-25, and page 8), there is evidence that the strain disclosed by Iuchi et al. which has a deletion of the arcA gene would inherently have improved production of a target substance synthesized via the tricarboxylic acid cycle as compared to a wild type γ-proteobacterium.

Applicant's arguments filed 9/12/05 and 6/10/05 have been considered, but have not been found convincing.

Applicant has argued that although Iuchi discloses arcA gene disrupted strains, these strains "do not have an ability to produce a target substance synthesized via the tricarboxylic acid cycle in an amount more than an amount of the substance produced by a wild-type bacterium. In contrast, the strains used in the Examples of the present specification are modified to have an ability to produce a target substance synthesized via the tricarboxylic acid cycle. That is the WC196 strain disclosed in Example 2 is an L-lysine-producing mutant strain as described In page 9, lines 23-24 of the specification, and the MG1655ΔsucA strain in which sucA gene is disrupted is an L-glutamic acid-producing strain" (page 7 of the arguments). However, contrary to applicants arguments, it is maintained that the strain disclosed by Iuchi et al. does have the ability to produce target substances, including amino acids, via the tricarboxylic acid cycle. It is clear that bacteria such as E. coli possess the enzymes of the tricarboxylic acid cycle, and produce target substances such as amino acids via this cycle, as taught in the instant application. There is evidence that the improved ability to produce such target substances would inherently result from the mutation or deletion of the arcA gene, since

the instant application teaches that the ArcA protein represses synthesis of said TCA cycle enzymes, and further teaches that deletion of said gene results in increased levels of these enzymes. Increased levels of these biosynthetic enzymes would result in increased levels of "target substances" produced by these enzymes. Iuchi et al. disclose at Table 2 that the levels of enzyme activity of the arcA$^-$ mutant strain are increased when compared to the wild type parent. Therefore, there is reason to believe that the mutant arcA strain disclosed by Iuchi et al. would inherently possess the property recited in the claim of improved levels of target substances when compared to the wild-type (unmodified) strain. Furthermore, the instant specification itself teaches that mutation or deletion of the arcA gene results in increased levels of production of the "targeted substances" (page 3, lines 16-26), and therefore, the strain disclosed by Iuchi et al. which is arcA$^-$ would inherently produce higher levels of such targeted substances when compared to the wild type strain. There is no disclosure in the instant specification teaching that this property is limited to the WC196 or the MG1655ΔsucA strains, or similar strains (see page 6 of the specification). For these reasons, the rejection is maintained.

Claims 1-3 and 5-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Nystrom et al. (EMBO J., Vol. 15, No. 13, pp. 3219-3228, 1996) (previously cited).

This rejection is maintained essentially for the reasons made of record in the previous Office actions, mailed 2/10/05, slightly modified to take into consideration applicant's amendments to the claims filed 9/12/05.

Nystrom et al. disclose E. coli strain comprising a deletion of the arcA gene, in which the ArcA protein does not function normally (see page 3220, right column – page 3221, end of right column). Since it is known that γ-proteobacterium such as E. coli possess the tricarboxylic acid cycle, and further, that the deletion of the arcA gene causes the derepression of the enzymes of said tricarboxylic acid cycle and the increase in production of products of the tricarboxylic acid cycle (see specification pages 2, lines 11-16; page 3 lines 10-25, and page 8), there is evidence that the strain disclosed by Nystrom et al. which has a deletion of the arcA gene would inherently have improved production of a target substance synthesized via the tricarboxylic acid cycle as compared to a wild type γ-proteobacterium.

Applicant's arguments filed 9/12/05 and 6/10/05 have been considered, but have not been found convincing.

Applicant has argued that although Nystrom et al. discloses arcA gene disrupted strains, these strains "do not have an ability to produce a target substance synthesized via the tricarboxylic acid cycle in an amount more than an amount of the substance produced by a wild-type bacterium. In contrast, the strains used in the Examples of the present specification are modified to have an ability to produce a target substance synthesized via the tricarboxylic acid cycle. That is the WC196 strain disclosed in Example 2 is an L-lysine-producing mutant strain as described In page 9, lines 23-24 of the specification, and the MG1655ΔsucA strain in which sucA gene is disrupted is an L-glutamic acid-producing strain" (page 7 of the arguments). However, contrary to applicants arguments, it is maintained that the arcA$^-$ mutant strain disclosed by

Nystrom et al. does have the ability to produce target substances via the tricarboxylic acid cycle. It is clear that bacteria such as E. coli possess the enzymes of the tricarboxylic acid cycle, and produce target substances via this cycle. In Figure 3 of Nystrom et al., the levels of enzymes of the TCA cycle are shown in the wild type strain and in the arcA$^-$ mutant strain, and the levels of the TCA cycle enzymes are higher in the arcA$^-$ mutant strain. Increased levels of these biosynthetic enzymes would result in increased levels of "target substances" produced by these enzymes. Therefore, there is reason to believe that the mutant arcA$^-$ strain disclosed by Nystrom et al. would inherently possess the property recited in the claim of improved levels of target substances when compared to the wild-type (unmodified) strain. Furthermore, the instant specification itself teaches that mutation or deletion of the arcA gene results in increased levels of production of the "targeted substances" (page 3, lines 16-26), and therefore, the strain disclosed by Nystrom et al. which is arcA$^-$ would inherently produce higher levels of such targeted substances when compared to the wild type strain. There is no disclosure in the instant specification teaching that this property is limited to the WC196 or the MG1655ΔsucA strains, or similar strains (see page 6 of the specification). For these reasons, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NANCY VOGEL, PH.D.
PATENT EXAMINER